claims 10-18 and 23. The latter set of claims to screening methods has been allowed.

The Rejection of Claims 1-9 and 19-22 Under 35 U.S.C. § 103(a)

Claims 1-9, and 19-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Morales (*Oncogene*, 2000, vol. 19, pp. 403-409) and Zur et al. (*EMBO*, 2001 Feb 15, vol. 20, pp. 792-801) in view of Lengauer et al. (*Nature*, 1998, vol. 396, pp. 643-649). Applicants respectfully traverse.

Claims 1-9 and 19-22 each recite a homozygous securin-defective cell line. Claims 1-4 are drawn to an isolated and purified homozygous securin-defective human cell line. Claims 5-9 and 19-22 are drawn to a pair of isogenic mammalian cell lines in which a first cell line is homozygous securin-defective and a second cell line is securin-proficient.

To reject claims under 35 U.S.C. § 103(a), the Patent Office must meet three criteria.

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claimed limitations.

M.P.E.P. § 2143. It is respectfully submitted that the Patent Office has failed to meet the first criterion in making its *prima facie* case of obviousness.

In determining patentability of a claimed invention, the teachings of the cited references are considered as a whole, including portions that lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). It is the prior art that must suggest the desirability and thus the obviousness of making the combination. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) citing *Lindemann*

Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462 (Fed. Cir. 1984). The mere fact that the prior art may be modified in the manner suggested by the Patent Office does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch* 972 F.2d 1260, 1266 (Fed Cir. 1992). The Patent Office has failed to identify any motivation in the cited references as a whole that would suggest the desirability and thus the obviousness of making the invention of claims 1-9 and 19-22.

The Patent Office cites Morales and Zur for teaching that overexpression of securin results in a tumorigenic phenotype. (Paper 9, page 3, line 6.) The final Office Action states that one of ordinary of skill in the art would have been motivated to arrive at the claimed homozygous securin-defective cell line in order to have a control cell that is devoid of any basal securin expression for comparison to a wild type heterozygous cell line. (Paper 9, page 3, lines 5-8.)

The asserted motivation to "have a control cell that is devoid of any basal securin expression for comparison to a wild type heterozygous cell line," is without basis in the teachings of either Morales or Zur. Morales teaches only cell lines with wild type securin expression. (See page 408, first column, "*Cell culture and lysis*.") Morales suggests mutagenizing *Xenopus* securin to produce proteins with substitutions at serine residues to study protein phosphorylation. "The possibility that the phosphorylation of other serine in *Xenopus* have the same role that phosphorylation of Ser^{165} in human PTTG (securin) needs further investigation." (Page 407, second column, lines 50-53.) But Morales does not teach or suggest a cell line that is devoid of basal securin expression.

Zur teaches cells transfected with expression vectors encoding wild type or a non-degradable but functional variant of securin. (Page 796, second column, lines 14-17.) Zur does

not suggest mutagenizing securin to make nonfunctional securin or modifying securin expression to form a cell line which is devoid of basal securin expression. Thus, neither Morales nor Zur suggest producing cell lines that are devoid of basal securin expression.

Furthermore, Morales and Zur do not teach or suggest the desirability of developing any new control cell line, much less a control cell that is devoid of securin expression. Each of Morales' experiments is controlled without use of the control suggested by the Patent Office. Morales compared securin expression in serum-starved and growth-arrested cells to control cells grown in 10% serum. (Page 404, second column, line 13 to page 405, first column, line 12; See also page 404, Figure 1 legend, line 4.) Morales also compared securin expression in cells arrested in each of the different phases of the cell cycle using a non-cycling control protein whose expression is not altered during the cell cycle as a standard. (Page 405, column 1, lines 17-22; Figure 2 legend, lines 5-7.) Morales also compared securin phosphorylation in cells treated with butyrolactone I to control cells not treated with butyrolactone I. (Page 407, first column, lines 7-12; Figure 7.) In each experiment, Morales employed controls. Morales does not teach or suggest a need for a further population of control cells devoid of securin expression.

Zur also employed controls in each of his experiments. Zur compared securin expression in cells at different stages of the cell cycle. (Page 794, second column, lines 5-7.) Zur compared securin expression in G_1-arrested cells treated with the proteasome inhibitor ALLN to untreated control G_1-arrested cells. (Page 794, second column, lines 11-17.) Zur compared securin degradation in prometaphase-arrested cells treated with roscovitin to untreated control prometaphase-arrested cells. (Page 795, first column, lines 2-4.) Zur also compared chromatid separation in cells transfected to express a non-degradable securin to control cells that express only wild type securin. (Page 796, second column, lines 14-17.) Thus Zur employed appropriate controls in his experiments. Zur does not provide any teaching or suggestion of a need for a

further population of control cells devoid of securin expression. Thus, neither Morales nor Zur provides any teaching that would suggest the desirability of, and thus the motivation for, producing a homozygous securin-defective cell line.

Moreover, the teachings of Morales, Zur, and Lengauer, taken as a whole would lead one of ordinary skill in the art *away* from the claimed invention. The Office Action dated February 13, 2002 cited Lengauer as teaching that to test if a specific gene is responsible for chromosomal instability it is necessary to have an immortalized cell line in which the targeted gene has been deleted. (Paper 7, page 4, lines 16-22.) This suggestion, however, applies to genes that behave recessively. "When the candidate gene [suspecting of causing the CIN phenotype] is presumed to act recessively, targeted deletion can be used." (Page 647, second column, lines 13-14.) For genes that function dominantly Lengauer provides a different test: "When the candidate gene is presumed to act in a dominant-negative fashion, recapitulation of the CIN phenotype can be accomplished through exogenous expression of the mutant gene product." (Page 647, second column, lines 10-13.) Morales teaches that the CIN phenotype is associated with securin overexpression. (Page 407, column 2, lines 8-11.) Zur teaches that a non-degradable (accumulating) but functional variant of the securin protein causes the CIN phenotype. (Page 799, second column, lines 8-15.) Thus the cited art teaches that securin functions in a dominant fashion to generate the CIN phenotype. Therefore, to recapitulate the chromosomal instability phenotype, as suggested by Lengauer, one of ordinary skill in the art would have been motivated to produce a cell line that exogenously expresses securin, not one that is devoid of securin expression. The teachings of Lengauer combined with those of Zur and Morales would have led one of ordinary skill in the art *away* from the claimed invention. One of ordinary skill in the art considering the teachings of Morales, Zur, and Lengauer, as a whole, would not have been

motivated to generate a cell line that is defective in securin.

The combination of Morales, Zur, and Lengauer do not suggest the desirability of making the claimed homozygous securin-defective cell line. The combination, in fact, teaches away from the claimed subject matter.

Withdrawal of this rejection of claims 1-9 and 19-22 is respectfully requested, as a *prima facie* case has not been made.

Respectfully submitted,

Date: October 30, 2002

By: _____
Michelle L. Holmes-Son
Registration No. 47,660

BANNER & WITCOFF, LTD.
Eleventh Floor
1001 G Street, N.W.
Washington, D.C. 20001
(202) 508-9100